Diagnostic Utility of Immunoassays for Parathyrin in Hyper- and Hypocalcemic States

By strict definition, hyper- or hypocalcemia should be classified as either an increase or a decrease in the concentration of the physiologically active calcium component in blood—the ionized fraction. The commonly used definition, however, is either an increase or decrease in the measured total calcium concentration in serum after making an allowance for any variation in the simultaneously measured albumin concentration. The correct diagnosis is essential in any condition if the appropriate treatment is to be instituted; this is particularly true for patients with either hyper- or hypoparathyroidism.

Hypercalcemia, and particularly hyperparathyroidism, is a common differential diagnostic problem. Many patients are either asymptomatic or have only vague, nonspecific symptoms. Fisk et al. (1) reported that there appears to be a distinct difference in both the incidence and causes of hypercalcemia between the general population, or unselected series of outpatients, and hospital inpatients. They concluded from their review of the literature that the incidence of hypercalcemia in the general population, or unselected outpatients, ranged from 0.1% to 1.6%, while in general-hospital inpatients it ranged from 0.5% to 3.6%. Hyperparathyroidism appeared to be the most common cause in some of the reported series of general population or unselected outpatients, but not in others. Other causes that had been reported to occur with various incidences include the administration of thiazide diuretics, thyroid disease, milk-alkali or milk-drinker's syndrome, and immobilization. Malignancy is more common in general-hospital inpatients than in the general population, and in most series it is the most common cause of hypercalcemia. In malignancy-induced hypercalcemia the secretion of various humoral factors, which are released into the circulation by the primary malignant tumor and cause bone resorption, accounts for the increase in the calcium concentration. The humoral mechanisms involved in tumor-induced hypercalcemia include the secretion of a parathyroid-like peptide, prostaglandins of the E series, transforming growth factors, tumor-necrosis factors, interleukin 1, and vitamin D-like sterols (2, 3). The parathyroid-like polypeptide secreted by these tumors, which are of non-endocrine origin, appears to have some differences in its amino-acid sequence from the natural hormone, particularly in the carboxy-terminal and mid-molecule regions (3). Depending on the antiserum being used, the parathyroid-like peptide secreted by some malignant tumors may react in an immunoassay system and create confusion in the differential diagnosis of primary hyperparathyroidism.

Hyperparathyroidism—whether primary, secondary, or tertiary—may be defined as the hyperscretion of parathyrin which is manifested by an increase in the concentration in serum. Thus the diagnosis of hyperparathyroidism depends on measurement of the concentration of the hormone in serum. Hypoparathyroidism, which may be either complete or partial and either transient or permanent, may be defined as the hyposecretion of parathyrin in response to a hypocalcemic stimulus. The diagnosis of hypoparathyroidism is dependent on the inability to detect the presence of the hormone in serum, or an inappropriately low concentration, with concomitant significant hypocalcemia. A major clinical problem is the recognition of those patients with primary hyperparathyroidism and their differentiation from those with hypercalcemia ascribable to all other causes. Patients with primary hyperparathyroidism, particularly those who are asymptomatic, require neck surgery. Reported (4), more than 75% of patients with primary hyperparathyroidism appear to have asymptomatic disease. In health-screening programs, the incidence of subsequently surgically proven primary hyperparathyroidism varies from 1 to 4 per 1000 individuals screened. Hypertension is twice as common in hyperparathyroid patients as in the general population.

The measurement of parathyrin in serum by either an immunoreactive or other technique will eventually be the ultimate "gold standard" for the diagnosis of hyper- and hypoparathyroidism and their differentiation from all other states associated with either hyper- or hypocalcemia. The immunoassays currently available have not allowed this ultimate standard to be established. In an interlaboratory study a few years ago, attention was drawn (5) to the problems of assay of immunoreactive-parathyrin (i-PTH), and it was stated that "determination of i-PTH in serum samples is far from being a routine method when compared with radioimmunoassays for hormones like insulin, growth hormone, etc.; the difficulties being due to lack of standardized reagents and peculiarities in the metabolism of the hormone". The situation has not changed dramatically since then, and bedside assessment still plays an important role in the differential diagnosis of hypercalcemia (6). The problems with i-PTH assays have resulted in the use of other biochemical variables in clinical algorithms for the differential diagnosis of hypercalcemia (7, 8). Of importance among these biochemical variables are acid-base changes (9, 10), which reflect the actions of parathyrin on its target tissues.

The measurement and interpretation of i-PTH values are complicated by the presence of multiple immunoreactive fragments of parathyrin in the blood compartment. The intact hormone, which is secreted by the parathyroid glands, consists of an 84-residue chain of amino acids. On release from the gland into the circulation, the intact hormone undergoes cleavage, mainly in the liver, at about residues 33-34 or 36-37 to yield carboxyl (C) and amino (N) terminal fragments. The smaller N-terminal portion is the biologically active fragment; it has a very short half-life, only 2 or 3 min, and is rapidly cleared from the circulation. The larger fragment contains the mid-molecule and C-terminal portions; this fragment has a half-life measured in hours, and its clearance depends on the presence of normal renal function. The heterogeneity of parathyrin and its fragments has led to the development of a variety of assays—"intact," "N-terminal," "C-terminal," or "mid-molecule," depending on the specificity of the antisera used in the assay. In the
presence of normal renal function, the C-terminal and mid-molecule i-PTH assays that are currently available are of value in differentiating patients with hypercalcemia attributable to primary hyperparathyroidism from those with hypercalcemia attributable to all other causes. In a study reported in this issue [11], a significant correlation was found between peripheral and thyroid venous-blood samples by using a mid-molecule assay: no such correlation was found on using a C-terminal assay on both samples. These studies were performed in a small group, only 13 patients, all of whom had surgically proven primary hyperparathyroidism. If these results are confirmed in a larger group of subjects, they would provide evidence that the mid-molecule i-PTH assay of peripheral blood more accurately reflects hormone status in the venous drainage of the parathyroid gland, than does the C-terminal, and the findings may prove to be of diagnostic relevance.

The serum i-PTH value must be interpreted with the simultaneous serum calcium concentration. In primary hyperparathyroidism, the i-PTH value should either be above the upper limit of the normal reference interval, or, if within these limits, it should be inappropriate for the prevailing serum calcium concentration. In patients with hypercalcemia resulting from all other causes, i-PTH in serum should either be undetectable or suppressed. In patients with renal failure, C-terminal and mid-molecule assays are of limited, if any, diagnostic value, because these fragments, which are not biologically active, accumulate in the blood compartment. N-terminal assays have been mainly used in patients with impaired renal function and also for directly assessing the secretory status of the parathyroid glands in localization studies by means of selective neck-vein catheterization. The latter diagnostic technique should only be used for the localization of parathyroid adenomas in those patients who have undergone previous neck surgery and have either persistent or recurrent hypercalcemia. It should not be used in the differential diagnosis of hypercalcemia.

References

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